SOLVAY PHARMACEUTICALS

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Vice President
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July 17, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD. 20852

Re: Docket No. OOD-1278
Draft Guidance for Industry on Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment; Availability

On 19 May 2000 FDA issued a draft guidance for industry entitled, "Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment." This is a complicated issue and this guidance is the first step leading to approval of new treatments for female sexual dysfunction. Herein we are providing new comments on the draft guidance and recommend that additional public discussion should occur prior to the finalization of the guidance.

1.0 OVERALL CLINICAL POSITION

- The draft guidance identifies female sexual dysfunction as decreased sexual desire, decreased sexual arousal, dyspareunia, and persistent difficulty in achieving or inability to achieve orgasm. While these conditions are components of sexual dysfunction, an individual need not experience all four to be considered dysfunctional.

- Moreover, the guidance outlines the following events or encounters to be considered primary efficacy endpoints in pivotal clinical trials in the assessment of female sexual function:

  - Satisfactory sexual intercourse;
  - Sexual intercourse resulting in orgasm;
  - Oral sex resulting in orgasm; and
  - Partner-initiated or self-masturbation resulting in orgasm.

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- The four proposed efficacy endpoints do not adequately address decreased sexual desire or decreased sexual arousal. While it is scientifically prudent to use objective efficacy endpoints, they may neglect some critical treatment effects. This is applicable when assessing conditions with a psychological aspect such as the desire component of female sexual dysfunction. The draft guidance assumes a sequential or causal relationship between sexual desire and activity. However, sexual activity alone does not adequately measure intrinsic desire. Female sexual activity is dependent upon many variables including; a partner, partner's health, interest or function, as well as relationship dynamics that may not be conducive to increased frequency of sexual encounters. We believe it is important to assess internal measures of desire in women, such as thoughts or fantasies, as well as actual sexual frequency couched with what the woman reports as her 'ideal' measure of frequency.

- Solvay Pharmaceuticals maintains that the target population of female patients might be in long-term relationships with established patterns of sexual behaviors. Sexual frequency in a long term relationship remains relatively stable despite interventions, and this frequency is often primarily determined by the male partner, not the female. In these cases, frequency of sexual encounters may not have dropped dramatically even though the woman may complain of a lack of or low sexual desire, since many women continue to participate in sexual activity to please their partners, despite the fact that they have no interest in sex. Therefore, the goal of treatment for all women at any age, but especially after the age of 50 years, may not be to maintain or to increase frequency but rather to derive enjoyment from the sexual experience.

2.0 PROPOSED PRIMARY EFFICACY ENDPOINTS

- Female sexual response is a complex psychological and physiological process. Though there are provisions within the current guideline for studying desire disorder with questionnaires, diagnostic scales, and other instruments, we propose that the ultimate endpoint NOT be orgasm or sexual encounters. Instead, we recommend that validated tests of intrinsic desire be considered as primary efficacy, with quantitative data as secondary or supportive. We believe that measurements of desire are appropriate primary efficacy endpoints for a therapy intended to treat female sexual dysfunction. These measurements should be multidimensional assessments, including measures of receptivity (satisfaction with frequency of sexual contacts/activity, arousal, orgasm-latency, intensity) and libido/desire (sexual fantasies/thoughts). The statistical requirements for quantification can be addressed by translating an 'event log' (daily diary) into 'objective' measures, such as the percent of women who have shown an increase in desire.

- Solvay Pharmaceuticals believes that examples of appropriate and validated scales are the Sexual Energy Scale (SES)[1], and the Changes in Sexual Functioning Questionnaire (CSFQ)[2].

Sincerely,

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[1] J. K. Warnock, M.D., Ph.D., J. C. Bundren, M.D., and D. W. Morris, M.A., "Female Hypoactive Sexual Desire Disorder Due to Androgen Deficiency: Clinical and Psychometric Issues", *Psychopharmacology Bulletin*, Vol. 33, No. 4, 1997, 761-766.

[2] A. H. Clayton, M.D., E. L. McGarvey, Ed.D., G. J. Clavet, Ph.D., and L. Piazza, M.D., "Comparison of Sexual Functioning in Clinical and Nonclinical Populations Using the Changes in Sexual Functioning Questionnaire (CSFQ)", *Psychopharmacology Bulletin*, Vol. 33, No. 4, 1997, 747-753.

Female Hypoactive Sexual Desire Disorder Due to Androgen Deficiency: Clinical and Psychometric Issues

Julia "Jill" K. Warnock, M.D., Ph.D.,[1] J. Clark Bundren, M.D.,[2] and David W. Morris, M.A.[3]

Abstract

Menopause, surgical or naturally occurring, with reduced or deficient ovarian functioning has a major impact on morbidity and mortality in mid to late life. In particular, a growing body of literature is focusing on the role of androgens in maintaining women's health and emotional well-being. Further study is needed in the administration of physiologic levels of testosterone replacement therapy as an adjustment to estrogen replacement. The Sexual Energy Scale was developed to provide an objective means of measuring the change in a patient's subjective experience of vitality/sexual energy with androgen replacement therapy. The scale also provides a clinical indication for androgen replacement dosage adjustment. Advantages in using low doses of methyltestosterone in women with hypoactive sexual desire disorder are discussed.

Introduction

In 1990, 591,000 hysterectomies were performed in the United States; approximately 45 percent were performed with bilateral oophorectomies. Thus, by the age of 60, about 1 out of every 3 women will have had a hysterectomy (American College of Obstetricians and Gynecologists 1992). Considering the prevalence of hysterectomies and oophorectomies, it is important to understand the impact of these surgical procedures on a woman's physical health, sexual functioning and quality of life, especially in light of substantially increased life expectancy. Menopause, surgical or naturally occurring, with reduced or deficient ovarian functioning is increasingly believed to play a significant and even pivotal role in the cause of short-term and long-term disorders and diseases in women (Sherman 1993). Medical research revealed the potential of ovarian hormone deficiency to have a major impact on morbidity and mortality in mid to late life. An oophorectomy increases a woman's risk for coronary artery disease (Bush 1990), osteoporosis (Richelson et al. 1984), and genitourinary atrophy (Cutler & Garcia 1984). Hormone replacement therapy (HRT) requires the clinician to choose, typically, the lowest estrogen doses capable of providing adequate protection against osteoporosis and relief of menopausal symptoms, and to use synthetic or semi-synthetic progestational agents for endometrial protection from hyperplasia and adenocarcinoma in women who have a uterus. However, a growing body of research is focusing on the role of androgens in maintaining a woman's health and emotional well-being (Andrews 1994; Rosenberg et al. 1997).

The Role of Testosterone in Female Physiology

Recent investigations demonstrate the role of androgens in female sexual behavior. A woman's libido depends on many environmental and hormonal factors, but evidence supports testosterone as the hormone of sexual drive in females (Sands & Studd 1995). Testosterone receptors are concentrated in the normal female brain; a deficiency in testosterone results in a global loss of sexual desire, decreased sensitivity to sexual stimulation in the nipples and in the clitoris, decreased arousability and capacity for orgasm, loss of muscle tone, diminished vital energy, thinning and loss of pubic hair, and dry skin (Rako 1996).

Women whose ovaries have been surgically removed can develop dramatic symptoms of both estrogen and testosterone deficiency (Rako 1996). Most of the premenopausal androgens are produced directly by the ovary or produced as androgen precursors that are subsequently converted to androgen in the periphery. Both testosterone and, to a lesser extent, androstenedione are significantly lower following oophorectomy (Longcope 1988). The postmenopausal ovaries lose about 50 percent of their total androgen production after menopause, whereas women post-oophorectomy have an even more marked reduction in their overall androgen complement (Longcope et al. 1982).

Testosterone Replacement Therapy

Just as estrogen replacement therapy is an established preventive measure for reducing fractures, the role of androgens in maintaining bone health is emerging. Androgen receptors are found in osteoblasts and the combination of estrogen and androgens actually increases bone mass (Gelfand 1994).

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Davis and colleagues (1995) found that postmenopausal women treated with combined estradiol and testosterone implants showed a greater increase in bone mineral density in the hip and lumbar spine than those treated with estradiol implants alone. Greater improvement in sexuality was also observed in the participants of this study with combined therapy, supporting the therapeutic use of testosterone for diminished libido in postmenopausal women.

There is a growing body of literature demonstrating the importance of androgen administration in improving libido in women with a deficiency in testosterone. Controlled studies on oophorectomized women have shown that the combination of estrogen and testosterone hormone replacement results in improved sexual desire, more sexual fantasies, and improved mood and energy (Sherwin 1985; Sherwin et al. 1985; Sherwin & Gelfand 1987). It is important for investigators and clinicians to note that sensitivity to testosterone varies with each individual. Two women with identical blood testosterone levels may experience different degrees of testosterone effect. Genetically determined differences in the number of testosterone receptors may be one factor that accounts for this (Rako 1996). Another factor that may affect the availability of free testosterone (free to produce effect on tissues) is estrogen. Estrogen stimulates the production of sex hormone binding globulin (SHBG). Since testosterone is carried on this protein, when more SHBG is produced, less testosterone is free or available to act on cells. Thus, supplementary (exogenous) estrogen may actually decrease the availability of free testosterone, potentially causing the symptoms of testosterone deficiency (Rako 1996). Nathorst-Böös and colleagues (1993) found, as expected, the highest levels of SHBG levels in the oophorectomized women receiving estrogen replacement therapy (ERT). Thus, these women were found to have the lowest levels of free testosterone and had the lowest scores regarding pleasure from intercourse. These investigators suggest that increased SHBG levels as a consequence of ERT may be particularly unfavorable for women in whom androgens after oophorectomy are already low. Further, Nathorst-Böös and co-workers suggest that androgens may be a useful supplement to ERT in oophorectomized women.

Risks of Testosterone Replacement

Concerns about testosterone replacement include masculinizing side effects, liver tumors and transaminase dysfunction, and adverse effects on lipids. The masculinizing side effects, such as very mild hirsutism, are dose dependent. This side effect generally occurs only in 15 to 20 percent of women who obtain supraphysiologic levels of testosterone (which occurs occasionally with implant therapy). The side effect is reversible upon drug discontinuation (Gelfand 1994). Voice changes and clitoromegaly are rare adverse effects (Sands & Studd 1995).

Liver dysfunction was primarily noted in patients who were taking very high doses of methyltestosterone who were female-to-male transsexuals. These doses were commonly 10 to 40 times higher than doses administered to oophorectomized women for testosterone replacement. Westaby and colleagues (1997) failed to demonstrate any adverse liver effects of methyltestosterone administered at standard doses (1.25 mg to 10 mg).

The traditional view is that androgens have an atherogenic effect. Part of this view stems from the fact that men are susceptible to heart disease at an earlier age than women. Studies assessing the effects of the addition of testosterone to estrogen have been inconsistent. Farish and colleagues (1984) found that testosterone prevented the rise in high-density lipoprotein cholesterol seen in the group receiving estrogen alone. Other investigators found no adverse effects of testosterone on the lipid profile (Gambrell & Teran 1991; Sherwin et al. 1987). Watts and colleagues (1995) noted that both the estrogen-only group and the estrogen-androgen-treated group demonstrated a significant fall in cholesterol, high density lipoprotein cholesterol, and triglycerides. For the latter group, the low density lipoprotein rose 2 percent at 24 months of treatment. Thus, the lower physiologic levels of testosterone replacement do not appear to have significant adverse effects. However, the potential for androgen replacement therapy to be a valuable adjunct to estrogen replacement is significant. Testosterone replacement appears to significantly enhance the total health and sexual functioning of selected women.

Clinical Evaluation for Androgen Replacement

Rosenberg and colleagues (1997) note four groups of women typically considered for estrogen-androgen therapy. The first group consists of women who have not achieved satisfactory relief for vasomotor symptoms from estrogen-only HRT. The second set of women who may benefit are those who have had their ovaries removed and no longer produce clinically useful amounts of estrogen and androgens. The third group of female candidates for testosterone replacement are those who are at risk for osteoporosis. Last, the fourth group are those women who have received estrogen-only HRT with unsatisfactory sexual function due to decreased libido. Rosenberg and colleagues (1997) further note that adequacy of androgen replacement must be judged by the patient's clinical response. To better evaluate in a clinical setting the adequacy of androgen replacement, a simple easy to administer scale was developed.

Sexual Energy Scale

The Sexual Energy Scale (SES) provides an objective means of measuring the patient's report of their subjective experience of vitality/sexual energy. When discussing the concept of vitality/sexual energy with the patient, the patient is instructed to note that the concept is more than the actual number of times of intercourse or masturbation per week. It includes sexual dreams, sexual fantasies, sensations of genitals, genital tension, and appetite for sexual experience. The purpose of the scale is to assess her lost familiar experience of sexual desire and vital energy, as well as to assess improvement following androgen replacement. The scale is based on a visual analog model of subjective experience. Each patient who presents as a potential candidate for androgen replacement is administered the following scale to assess their intra-individual experience with changes in their sexual energy level (see Appendix I). The patient rates her current sexual energy level on a scale of 1 to 10, with 1 being the lowest sexual energy level that she personally has experienced as an adult and 10 being the highest. The patient repeats the SES at each visit. In addition, the Sexual Energy Change Scale is administered at followup visits. This scale rates the patient's improvement on a scale of 0 (my sexual energy is worse than before hormone therapy started) to 5 (I have complete relief of all my problems with sexual energy level compared with before the hormone therapy started) (see Appendix II).

Screening Evaluation

Patients are evaluated in a community-based medical-school-affiliated office practice of gynecology, specializing in reproductive medicine. All patients who have undergone a hysterectomy with bilateral oophorectomy and who have adequate estrogen replacement therapy (serum estradiol levels between 100 to 200 pg/ml) with complaints of decreased sexual desire, lack of zest, or decreased sexual response are evaluated. Patients receive a physical examination and undergo routine laboratory tests including a complete blood count, lipid profile, liver enzymes, thyroid function, and free and total testosterone. The patients who qualify for a diagnosis of female hypoactive sexual desire disorder due to androgen deficiency must have a free testosterone less than 2.0 pg/ml and an SES initial rating of 1, 2, or 3. In addition, all patients referred or who present for androgen replacement are administered the Primary Care Evaluation of Mental Disorders (PRIME MD; Spitzer et al. 1993). The PRIME MD is a screening procedure that facilitates rapid and accurate recognition and diagnosis of mental disorders most commonly seen in adult patients in primary care settings. The PRIME MD is given in an attempt to eliminate common psychiatric disorders, such as major depression, which may affect a patient's report of sexual functioning.

Methyltestosterone Administration

Oral doses of micronized methyltestosterone (0.25 mg, 0.50 mg, and 0.75 mg tablets) are compounded at a local pharmacy (Saffa Pharmacy, 81st and Sheridan, Tulsa, OK) since these low doses are not available from a proprietary source. Patients who have undergone a hysterectomy with bilateral oophorectomy and who meet criteria for female hypoactive sexual desire (SES 1, 2, or 3 and a testosterone level less than 2.0 pg/ml) are started on 0.25 mg oral micronized methyltestosterone. At each followup visit, the patient is interviewed and she again completes the SES. The dose of methyltestosterone is increased if the SES is less than 5. No increase is made for an SES greater than 8. Clinical judgment is used when the SES is between 5 and 8. Titration increases of methyltestosterone are generally in increments of 0.25 mg.

Discussion

Androgen replacement in women is a neglected area of medical practice (Sands & Studd 1995). While formal results of this intervention are not yet available, the preliminary clinical experience of this open-label investigation seems promising. In his presidential address to the 12th Annual Meeting of the American Gynecological and Obstetrical Society, Andrews (1994) noted that most studies currently reporting on testosterone replacement use either long-acting injected material or oral preparations containing methyltestosterone in doses that achieve supraphysiologic serum levels. He further noted that

> ". . . evidence relating a positive effect on mood and sexual satisfaction to serum testosterone levels in patients with substantially lowered testosterone levels suggest the importance of determining whether testosterone replacement that achieves physiological levels would also produce similar measurable benefits. . ." p. 965.
>
> "Current information persuades me that testosterone designed to achieve physiologic serum levels should be part of hormone replacement after oophorectomy." p. 965.

Because of the paucity of research using physiologic levels of testosterone replacement, a systematic open-label clinical trial was initiated. Our clinical experience and others (Rako 1996) has noted that oral methyltestosterone may be effective at doses of 0.25 to 0.80 mg per day with most women benefiting from 0.3 to 0.6 mg. Note that there are no androgen-containing compounds available in the United States at these low dosages. There are several advantages to using oral methyl-

testosterone, although there are other compounding options available (e.g., testosterone gel, oral micronized testosterone, and testosterone troche). One advantage of oral methyltestosterone is flexibility in dosing, which enables the clinician to individualize treatment. Additionally, methyltestosterone is not as readily converted to estrogen as is natural testosterone. Thus, hypothetically, it is hoped that the potential to increase SHGB is avoided.

The evidence is accumulating that both oophorectomized women and many patients undergoing natural menopause develop physical and behavioral symptoms that suggest androgen deficiency. Physiologic androgen replacement therapy may improve sexual desire and functioning and increase vital energy with a sense of well-being. While the efforts described here are preliminary, it is part of a growing body of research that demonstrates a commitment to improve the quality of life of women as they pass through the postreproductive third of their lives. Further research needs to include well-controlled observational studies and rigorously designed clinical trials investigating the benefits of androgen therapy in women. Clearly there is a need for further studies of different routes of administration and different forms of androgens.

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Appendix I

SEXUAL ENERGY SCALE (SES)

On a scale of 1 to 10, with *1 being the lowest sexual energy level* you have experienced in your adult life and *10 being the highest sexual energy level* you have experienced in your adult life, rate your *current energy level*. Please circle the number that indicates *your current energy level.*

Patient ID: _____ Date: _____

Study ID: _____ Med Info: _____

LOWEST SEXUAL ENERGY LEVEL IN ADULT LIFE **HIGHEST SEXUAL ENERGY LEVEL IN ADULT LIFE**

1 2 3 4 5 6 7 8 9 10

Appendix II

CATEGORY SCALE - ENERGY LEVEL CHANGE

Please circle the number below which best describes your sexual energy level *right now*:

0 My sexual energy level is **WORSE** than before the hormone therapy (methyltestosterone) started.

1 There is **NO CHANGE** in my sexual energy level compared to before the hormone therapy (methyltestosterone) started.

2 There is a **SLIGHT IMPROVEMENT** in my sexual energy level compared to before the hormone therapy (methyltestosterone) started.

3 There is a **MODERATE IMPROVEMENT** in my sexual energy level compared to before the hormone (methyltestosterone) therapy started.

4 There is a **LOT OF IMPROVEMENT** in my sexual energy level compared to before the hormone therapy (methyltestosterone) started.

5 I have **COMPLETE RELIEF** of all problems with my sexual energy level compared to before the hormone therapy (methyltestosterone) started.

Patient ID: _____ Date: _____

Sexual Energy Scale (SES): A Simple, Valid Screening Tool for Measuring Sexual Dysfunction

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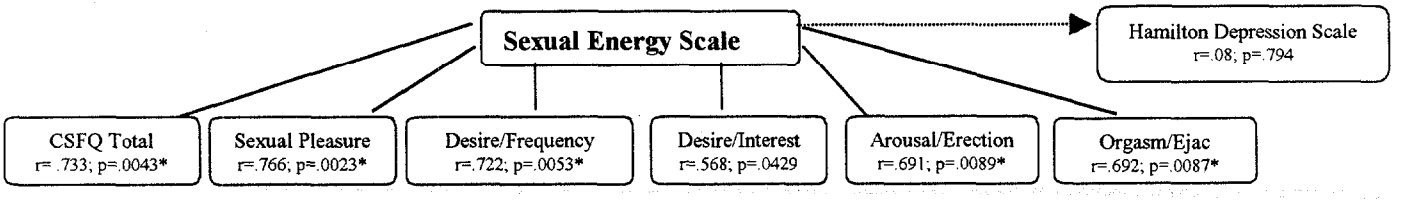
Background: Sexual dysfunction (SD) is gaining increased attention as a public health concern. Laymann et al (1999) documented a 43% prevalence of SD in women and a 33% prevalence of SD in men. Progress in the research and treatment of SD is hampered by the lack of practical and valid psychometric instruments. The Sexual Energy Scale (SES) provides a simple, easy and objective means of assessing the patient's lost familiar experience of sexual desire and vital/sensual energy. The SES also measures changes in sexual function following an intervention. The scale is a visual analog model in which the patient rates their current sexual energy level on a scale of 1 to 10.

Methods: To determine concurrent validity, the Changes in Sexual Functioning Questionnaire (CSFQ) and the SES were completed by a series of psychiatric patients (N=17) who presented for treatment of medication induced SD. The CSFQ is a 32 item structured interview designed to measure illness and medicated-related changes in sexual functioning with reliable and valid psychometric properties. Correlation coefficients were calculated for SES and the CSFQ total and subscales. In addition, the patients were readministered both the SES and the CSFQ 1 month after treatment for their sexual dysfunction. Correlation coefficients between the change score for the SES and the change scores for CSFQ total and subscale scores were also obtained.

Results: Figure 1 shows the correlation coefficients between the SES and the CSFQ and subscales.



The change scores on the SES correlated significantly with change scores on the following CSFQ scales: SES & CSFQ global score r=.679; p=.01; SES & Desire/Freq r=.647; p=.01; SES & Desire/Interest r=.66; p=.01; SES and Arousal r=.625; p=.02.

Conclusions: The SES indicates good concurrent validity with the CSFQ. Discriminate validity is supported by the low correlation between the SES and the Hamilton Depression Scale. The SES can be used by clinicians as an easy valid tool in the assessment of SD.

Comparison of Sexual Functioning in Clinical and Nonclinical Populations Using the Changes in Sexual Functioning Questionnaire (CSFQ)

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Abstract

The Changes in Sexual Functioning Questionnaire (CSFQ), a structured interview/questionnaire designed to measure illness- and medication-related effects on sexual functioning, is presented with initial evidence of its clinical usefulness in differentiating between those who have sexual dysfunction and those who have no dysfunction. Individuals from clinical and nonclinical samples completed the CSFQ. The sample groups were compared on mean scores on the CSFQ and its subscales. Comparative findings indicate that psychiatric patients diagnosed with a mood disorder have significantly lower sexual functioning when compared with nonpsychiatric outpatients, medical students, and psychiatry residents combined. The CSFQ is a useful measure for assessing medication- or illness-related effects on sexual functioning in a systematic way.

Introduction

Psychiatric illness, particularly mood and anxiety disorders, can have a direct negative impact on sexual functioning (Teusch et al. 1995). In many cases, psychopharmacological treatment may improve sexual dysfunction related to the psychiatric illness. However, a number of medications used to treat illness and disease (e.g., psychiatric illness, hypertension, cancer) have themselves been associated with problems with sexual functioning attributable to the mechanisms of action of the specific drugs involved (Curry et al. 1994; Goldenberg et al. 1995). Drug-related sexual side effects among patients receiving treatment for psychiatric illness include altered libido (Mitchell & Popkins 1983; Segraves 1988), impotence (Segraves 1989), anorgasmia (Sangal 1985; Segraves 1995), delayed or retrograde ejaculation (Feiger et al. 1996; Schwarcz 1982; Segraves 1989), priapism (*Dista* 1994; Thompson et al. 1990; Yeragani & Gershon 1987), and spontaneous (McLean et al. 1983; Modell 1989) or painful orgasm (Aizenberg et al. 1991; Balon et al. 1993).

While medication to treat psychiatric illness has been associated with sexual dysfunction, sexual functioning has also been shown to improve with psychotropic medications that increase libido (Gartrell 1986; Sullivan 1987, 1988), reverse sexual disorders (Assalian 1988; Montorsi et al. 1994; Power-Smith 1993), treat the psychiatric illness, or reverse the sexual dysfunction caused by other psychotropic medications (Gitlin 1995; Jacobsen 1992; Othmer & Othmer 1987*a*; Price & Grunhaus 1990; Walker et al. 1996). These effects are specific to the mechanisms of action of each drug, including dopamine agonism (Walker et al. 1996), serotonergic effects, cholinergic-adrenergic modulation (Sorscher & Dilsaver 1986), hormonal interactions including testosterone and prolactin (Wein & Van Arsdalen 1988), sacral parasympathetic function, and possibly sympathetic pathways and limbic arousal (Harrison et al. 1986).

Assessments of negative changes in sexual function secondary to psychiatric illness or related to treatment have primarily relied on informal feedback from patients, resulting in underestimations of the prevalence of sexual dysfunction (Harrison et al. 1986; Mitchell & Popkins 1983; Monteiro et al. 1987). The use of self-report questionnaires to specifically assess sexual dysfunction associated with illness has improved reporting. The Derogatis Sexual Function Inventory (DSFI) (Derogatis 1975; Derogatis & Melisaratos 1979) has been found to be particularly useful in clinical populations (Conte 1983). Other questionnaires that address one or more separate factors of desire, arousal, and release include the Brief Sexual Function Questionnaire (Reynolds et al. 1988), the Sexual Function Questionnaire (Monteiro et al. 1987), and an unnamed 16-item analog scale (Othmer & Othmer 1987*b*). In addition, structured interviews to evaluate sexual function have also been successful in producing more accurate estimates of the problem (Bolling 1994; Reading & Wiest 1984; Schiavi 1992; Seidman & Rieder 1994).

The instruments cited above are useful for their designed purposes. However, for the assessment of sexual function associated with psychiatric illness and medication effects, a brief instrument specifically constructed to obtain adequate illness-related information is needed. The Changes in Sexual Functioning Questionnaire (CSFQ) was developed to systematically track changes in sexual function in a clinical population that may experience specific or unusual sexual side effects following use of medications to alleviate psychiatric distress

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(Clayton et al. 1995). It may also be useful in other clinical populations.

Construction of the CSFQ

The CSFQ was designed to measure five aspects of sexual functioning: frequency of sexual activity, interest and desire for sex, degree of sexual pleasure, sexual arousal (measured by erection capability in men and vaginal lubrication and other physiological states in women), and sexual completion measured by one's ability to achieve orgasm and, in the case of men, ejaculation. These sexual states parallel those described in the *DSM-IV* and provide face validity for the instrument (American Psychiatric Association 1994; Anastasi 1988; Rosenthal & Rosnow 1984). Items related to the five sexual states are rated on 5-point Likert rating scales of degree of satisfaction (1=none; 5=great), frequency (1=never; 5=every day or always) and change (1=no change; 5=greatly improved or greatly worsened). The CSFQ measures satisfaction or problems within the five areas to indicate a profile of sexual functioning that reveals whether a clinically significant problem exists. Items regarding comorbid medical conditions, the patient's current medication use, alcohol and other recreational drug use, relationship status, and so on provide information for determining whether self-reported sexual difficulties are attributable to relationship- or stress-related issues rather than to illness or medication effects.

There are two versions of the CSFQ: a clinical interview version (CSFQ-I) and a gender-specific self-administered version, that is presented in a paper-and-pencil questionnaire format (CSFQ-F for females and CSFQ-M for males). The questionnaire version includes key items contained on the clinical interview version to provide an assessment of sexual functioning. In most clinical settings, the CSFQ is optimally used during an interview in which the clinician can review the items and response options with the patient. However, patients who are uncomfortable or extremely reluctant to discuss sexual issues can complete the measure without assistance as a paper-and-pencil questionnaire to be discussed later with the clinician.

The CSFQ contains 36 items for male respondents and 35 items for female respondents. The first 21 items apply to both men and women. (For a copy of the CSFQ-I, see Appendix A in Clayton et al. 1997, this issue, p. 739.)

Pilot Study

During the early development of the measure, an in-depth pilot study (Clayton et al. 1995) was conducted in a sample of 10 patients who were diagnosed with major depression and were being treated with a selective serotonin reuptake inhibitor. This study, which is described in a separate publication, supported the clinical utility of the CSFQ in tracking and measuring patient-specific changes in sexual function related to illness or treatment (Clayton et al. 1995). The patient's physician compared responses on the CSFQ for each patient over time to measure any change due to treatment or medication. The change scores on the CSFQ accurately differentiated global elements, changes associated with specific factors of sexual response, and medication-specific side effects over time. The pilot study demonstrated that the CSFQ could distinguish sexual dysfunction as a probable medication effect in patients who experienced therapeutic benefit from the antidepressant agent. Patients in the pilot study could be categorized into three groups: patients with increased libido without sexual dysfunction, patients who developed anorgasmia as a medication-emergent side effect, and patients with long-term sexual dysfunction unchanged by illness or medication. While the CSFQ presents itself as a clinically useful tool in detecting changes over time, from the onset of illness through the course of treatment, certain refinements to the instrument were made and an investigation of the validity and reliability of the instrument was conducted.

Validation of the CSFQ

Results from a validation study based on responses from two nonpatient samples are reported in a separate publication (Clayton et al. 1996) and in the preceding article in this issue (Clayton et al. 1997). Data were collected from two volunteer groups—medical students and psychiatry residents—on two separate occasions. The objectives were (1) to test the internal consistency of hypothetical constructs measured by the CSFQ, (2) to determine the stability of the responses on key individual items from the CSFQ over time in a normal population to provide a basis for a reliable comparison with a clinical population, and (3) to establish concurrent validity between constructs measured by the CSFQ and those derived from a well-validated measure of sexual functioning like the Derogatis Interview for Sexual Functioning—Self-Report (DISF-SR). Results indicate that the CSFQ assesses sexual functioning on five cohesive dimensions or factors[1] corresponding to the *DSM-IV* categories: Sexual Pleasure, Sexual Desire/Frequency, Sexual Desire/Interest, Sexual Arousal, and Sexual Orgasm. Each of the scales was found to have moderate to high internal consistency among males and females. The CSFQ also has high test-retest reliability: responses for key items that comprise the five factors are highly correlated at $Time_1$ and at $Time_2$. Findings also show that constructs mea-

[1]While preliminary analysis of the factor structure is promising, the factors mentioned here are not empirically derived. More data are being collected to ensure a sample including sufficient numbers of males and females to permit confirmatory analysis of the factors in the instrument by gender.

TABLE 1. Demographic Characteristics of Clinical and Nonclinical Participants.

	Nonclinical Sample			Clinical Sample
	Medical Students	Psychiatry Residents	Nonpsychiatric Outpatients	Depressed Patients
N	122	33	16	32
Gender:				
Male (*n*)	56% (68)	52% (17)	0% (0)	41% (13)
Female (*n*)	44% (54)	48% (16)	100% (16)	59% (19)
Race:				
Caucasian (*n*)	70% (85)	76% (25)	94% (15)	84% (27)
Non-Caucasian (*n*)	30% (37)	24% (8)	6% (1)	16% (5)
Marital Status:				
Single, never married (*n*)	76% (93)	36% (12)	0% (0)	31% (10)
Married (*n*)	14% (17)	42% (14)	63% (10)	41% (13)
Other (living with someone, divorced, separated,widowed) (*n*)	10% (12)	22% (7)	37% (6)	28% (9)
Mean age (standard deviation)	24.9 (2.8)	30.8 (4.4)	46.9 (9.7)	44.6 (10.3)
Age range	22-41 years	25-43 years	26-63 years	23-64 years
Percent involved in sexual relationship?(20)(*n*)	70% (85)	82% (27)	94% (15)	63% (20)

sured by the CSFQ are strongly correlated with certain DISF-SR scales (Clayton et al. 1996, 1997).

Purpose of the Present Study

The purpose of the present study is to illustrate the usefulness of the CSFQ in distinguishing between a clinical sample of patients being treated for affective disorders and a nonclinical sample with respect to problems in sexual functioning.

Method

Participants and Procedures

The following participants, comprising the nonclinical sample, were asked to complete the CSFQ questionnaire: 122 medical students who completed the CSFQ on two occasions 4 weeks apart; 33 psychiatry residents who completed the CSFQ on two occasions approximately 7 days apart; and 16 female outpatients at a women's health clinic who completed the CSFQ during a health check visit. The last group was screened for depression using the Beck Depression Inventory (Beck et al. 1961); patients indicating clinical levels of depression were excluded from the analyses. These women reported no other mental health problems.

In addition to the nonclinical samples, 32 patients from a psychiatric clinic at a major university were administered the CSFQ interview by a physician or clinician-rater just prior to medication treatment. These patients were evaluated with the affective disorders portion of the Structured Clinical Interview for the *DSM-III-R* with a psychotic screen (SCID; Spitzer et al. 1988), and were diagnosed with major depression (chronic or acute), dysthymia, or double depression. Most complained of sexual dysfunction as a result of their psychiatric illness. Table 1 presents the demographic characteristics of participants in each nonclinical and clinical group. Approval for this study was obtained from the University of Virginia's Institutional Review Board prior to data collection. Participants were informed that their participation was voluntary, that they had the right to refuse to answer any or all questions, and that their responses were confidential and would only be identified by a code number of their choice.

Results

Patients with clinical depression and other psychiatric illnesses often report decreased libido (Howell et al. 1987). Patients in the clinical sample had an independent evaluation of their psychiatric illness (e.g., depression). If the CSFQ was to be useful in determining sexual problems, it must be sensitive to specific sexual problems in this clinical population. As such, sexual functioning scores in the clinical sample would be expected to be lower (i.e., indicating more dysfunction) than those in the nonclinical sample, thus providing a criterion against which to test the usefulness of the CSFQ. To examine these differences, data collected from the depressed patient sample were compared with data collected from participants in the three nonclinical samples.

Mean comparisons were made to determine differences between the clinical and nonclinical samples on responses to the CSFQ, specifically scores measuring particular areas of sexual function. Table 2 presents mean total scores on the

TABLE 2. Mean Total CSFQ Score and CSFQ Subscale Scores For Clinical and Nonclinical Groups.

		Men			Women		
		Mean ± SD	*N*	95% CI	Mean ± SD	*N*	95% CI
Total CSFQ	Depressed patients	43.40 ± 4.50	10	40.18 – 46.62	34.00 ± 8.96	9	27.11 – 40.89
	Medical students	50.18 ± 3.15	40	49.17 – 51.18	43.48 ± 4.94	40	41.90 – 45.05
	Psychiatry residents	45.77 ± 4.57	13	43.01 – 48.53	43.47 ± 3.69	7	40.16 – 46.99
	Nonpsychiatric outpatients	n/a	n/a	n/a	39.17 ± 6.65	12	34.95 – 43.39
Sexual Desire/ Frequency	Depressed patients	7.23 ± 1.30	13	6.45 – 8.02	5.17 ± 1.72	18	4.31 – 6.02
	Medical students	8.22 ± 1.30	63	7.90 – 8.55	6.74 ± 1.56	54	6.32 – 7.17
	Psychiatry residents	7.53 ± 0.92	15	7.03 – 8.04	7.09 ± 1.64	11	5.99 – 8.19
	Nonpsychiatric outpatients	n/a	n/a	n/a	6.25 ± 1.55	12	5.27 – 7.23
Sexual Desire/ Interest	Depressed patients	9.54 ± 1.61	13	8.56 – 10.51	7.60 ± 1.64	15	6.69 – 8.51
	Medical students	11.21 ± 2.27	62	10.63 – 11.79	9.33 ± 2.27	54	8.71 – 9.95
	Psychiatry residents	11.00 ± 2.25	14	9.70 – 12.30	9.91 ± 1.70	11	8.77 – 11.05
	Nonpsychiatric outpatients	n/a	n/a	n/a	9.09 ± 2.59	11	7.35 – 10.83
Sexual Pleasure	Depressed patients	3.00 ± 0.94	10	2.33 – 3.67	2.80 ± 1.23	10	1.92 – 3.68
	Medical students	3.98 ± 1.15	50	3.65 – 4.31	4.05 ± 1.00	41	3.73 – 4.36
	Psychiatry residents	3.75 ± 1.13	16	3.15 – 4.35	3.50 ± 1.17	12	2.76 – 4.24
	Nonpsychiatric outpatients	n/a	n/a	n/a	3.40 ± 0.91	15	2.90 – 3.90
Sexual Arousal	Depressed patients	11.77 ± 2.74	13	10.11 – 13.43	9.69 ± 3.52	13	7.57 – 11.82
	Medical students	14.06 ± 1.19	67	13.77 – 14.35	11.28 ± 1.93	54	10.75 – 11.80
	Psychiatry residents	12.94 ± 1.84	16	11.96 – 13.92	11.50 ± 1.75	16	10.57 – 12.43
	Nonpsychiatric outpatients	n/a	n/a	n/a	10.21 ± 2.67	14	8.68 – 11.75
Sexual Orgasm	Depressed patients	11.54 ± 1.51	13	10.63 – 12.45	9.27 ± 2.87	11	7.35 – 11.20
	Medical students	13.19 ± 1.21	62	12.89 – 13.50	11.26 ± 2.31	53	10.63 – 11.90
	Psychiatry residents	12.07 ± 1.90	14	10.97 – 13.17	11.53 ± 1.92	15	10.47 – 12.60
	Nonpsychiatric outpatients	n/a	n/a	n/a	10.57 ± 1.56	14	9.67 – 11.47

NOTE: CSFQ = Changes in Sexual Functioning Questionnaire; CI = confidence interval; n/a = not applicable (there are no men in the fourth group).

CSFQ as well as mean scores on the subscales for each of the sample groups. A total score based on 14 items assessing current global sexual function was computed, as were subscale scores assessing function with respect to Sexual Desire/ Frequency (Items 11 and 19), Sexual Pleasure (Item 8), Sexual Desire/Interest (e.g., sexual fantasies or thoughts, watching erotic movies, reading erotic literature; Items 14, 20, and 21), Sexual Arousal (Items 22, 23, and 24), and Sexual Orgasm (Items 27, 28, and 30 for women; Items 28, 29, and 31 for men).

For men, the total score was computed by summing the responses to the above-mentioned items that assess current sexual functioning in the five areas. Two items—Item 27 ("How often do you have painful, prolonged erections?") and Item 32 ("How often do you have painful orgasms?")—were reverse-scored and also included in the total score. For women, items mentioned above under the five areas of sexual functioning were included in the total score. Item 25 ("How often do you become aroused and then lose interest?") and Item 31 ("How often do you have painful orgasms?") were reverse-scored and also included in the calculation. The total CSFQ score, for both men and women, can conceivably range from 14 to 70 points. The subscale scores were computed by summing the scores for the items that measured that particular area of sexual function.[2] One-way analyses of variance were performed, separately by gender, to determine whether there were any differences between the clinical and nonclinical samples on the total CSFQ score and the five subscale scores. *Post hoc* mean comparisons were done if the omnibus *F*-statistic was statistically significant at the .05 level of probability. Mean comparisons between each of the groups were assessed using the Scheffe test.

Total CSFQ Score

For men, comparisons were made between three groups—depressed patients, medical students, and psychiatry residents (there are no males in the fourth group, the nonpsychiatric outpatients). There is a significant difference among the three groups with respect to the total CSFQ score of global sexual function [$F(2,60)=16.94$; $p<.0001$]. Based on *post hoc* mean comparisons, the depressed patient group has a significantly lower mean score than the medical students. However, the scores of the depressed patients do not differ significantly from those of the psychiatry residents.

[2]Scale scores potentially range from 2 to 10 for Sexual Desire/Frequency; from 3 to 15 for Sexual Desire/Interest, Sexual Arousal, and Sexual Orgasm; and from 1 to 5 for Sexual Pleasure.

For women, comparisons were made between four groups—the medical students, the psychiatry residents, the depressed patients, and the female nonpsychiatric outpatients. With respect to the total CSFQ score, there is a significant difference among the four groups [$F(3,64)=7.49$; $p=.0002$]. Based on *post hoc* mean comparisons, the depressed patients have a significantly lower mean score than either the medical students or the psychiatry residents. Although the nonpsychiatric outpatients have a higher mean score than the depressed patients, the mean difference is not statistically significant.

CSFQ Subscales

Sexual Desire/Frequency. For men, the three groups differ with respect to sexual desire/frequency [$F(2,88)=4.49$; $p=.014$]. The depressed patients have the lowest mean score, followed by the psychiatry residents and then the medical students. Only the depressed patients and the medical students differ significantly from each other according to *post hoc* tests. Among women, there is a significant difference among the four groups on reported sexual desire/frequency [$F(3,91)=5.11$; $p=.0026$]. *Post hoc* tests show that the depressed patients have significantly lower mean scores than either the medical students or the psychiatry residents, but do not have significantly lower scores than the nonpsychiatric outpatients.

Sexual Pleasure. Males in the three groups also differ on reported degree of sexual pleasure experienced [$F(2,73)=3.20$; $p=.047$]. According to *post hoc* tests, the depressed patients have a significantly lower score than the medical students, but do not differ significantly from the psychiatry residents. For women, there is a significant difference on reported sexual pleasure [$F(3,75)=4.58$; $p=.0053$]. The medical students have the highest mean score, followed by the psychiatry residents, the nonpsychiatric outpatients, and then the depressed patients, who have the lowest mean score. *Post hoc* tests show that the depressed patients differ significantly from the medical students only.

Sexual Desire/Interest. For men, there is a significant difference among the three groups in terms of reported sexual desire or interest, including experiences with sexual fantasies [$F(2,86)=3.14$; $p=.048$]. *Post hoc* tests indicate that the depressed patients have a significantly lower mean score than the medical students, but not when compared with the psychiatry residents. Among women, there is a significant difference among the four groups with respect to reported sexual desire or interest [$F(3,87)=3.12$; $p=.030$]. The psychiatry residents have the highest mean, followed by the medical students, the nonpsychiatric outpatients, and then the depressed patients. However, *post hoc* comparisons between the four groups do not reveal any significant differences.

Sexual Arousal. There is a significant difference among the three groups for men on reported sexual arousal, specifically an ability to achieve and maintain an erection: [$F(2,93)=12.79$; $p<.0001$]. The medical students have the highest mean score, followed by the psychiatry residents, and then the depressed patients. *Post hoc* tests show that the depressed patients have a significantly lower mean score than the medical students, but do not differ significantly from the psychiatry residents. For women, there is a marginally significant trend for mean scores on reported sexual arousal—as indicated by vaginal lubrication—to differ among the four groups [$F(3,93)=2.48$; $p=.066$], with the depressed patients having the lowest mean score compared to the other three groups.

Sexual Orgasm. Males in the three groups differ on the measure of sexual orgasm, specifically the ability to achieve ejaculation and orgasm [$F(2,86)=9.89$; $p=.0001$]. According to *post hoc* tests, the medical students have a significantly higher score than either the psychiatry residents or the depressed patients. However, the last two groups do not have significantly different mean scores. With respect to women, there is a significant difference among the four groups on sexual orgasm [$F(3,89)=2.91$; $p=.039$]. Although the depressed patients have the lowest mean score, *post hoc* tests show no individual group comparisons that are significant.

Comparison Between Clinical and Nonclinical Samples

Contrasts (employing two-tailed *t*-tests) were performed, separately by gender, to determine whether there are mean differences between the depressed patient sample and the other nonclinical samples combined. Mean scores on each CSFQ for the clinical group (depressed patients) and for the combined nonclinical groups (medical students, psychiatry residents, and nonpsychiatric outpatients) are displayed separately for men and women in Figure 1. There are significant differences between the clinical and nonclinical samples, for men and women, on global sexual functioning (as indicated by the total CSFQ score) as well as within the five individual areas of sexual functioning. The depressed patient sample has a significantly lower score on the total CSFQ than the combined nonclinical sample, indicating diminished overall sexual functioning and satisfaction for both men and women. In comparison with the combined nonclinical groups, the depressed patient sample has significantly lower scores on all five scales: Sexual Desire/Frequency, Sexual Desire/Interest, Sexual Pleasure, Sexual Arousal, and Sexual Orgasm. This difference indicates that the depressed patients report significantly (1) less sexual activity; (2) less desire to engage in sex, including having less frequent thoughts about sex; (3) less overall pleasure experienced from sexual activity; (4) more problems associated with the ability to achieve and maintain arousal (or, for men, an erection); and (5) more problems associated with the ability to achieve sexual completion through orgasm (and, for men, ejaculation).

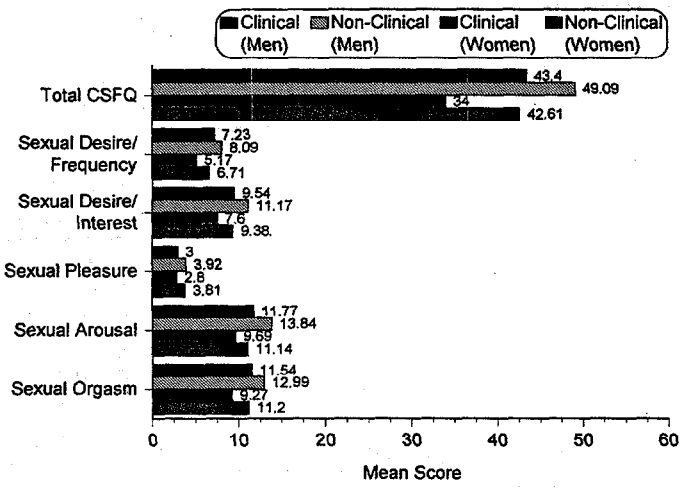

FIGURE 1. Mean total CSFQ scores and subscale scores between depressed patients (clinical) and combined nonclinical groups.

Discussion

The CSFQ is useful in assessing sexual functioning in both clinical and nonclinical samples. The measure reliably demonstrates diminished sexual functioning in a clinical sample of patients who were diagnosed with depression.

In the ongoing investigation of the CSFQ, data reported for certain analyses were collected first from a relatively homogeneous sample of young, well-educated adults. Further studies are in progress to investigate the validity and reliability of the CSFQ in larger nonpatient and patient samples that are more heterogeneous in terms of age, ethnicity, occupation, and educational level. Second, since patients may disclose more during a personal interview, possible differences in responses between patients who are interviewed and those who complete the questionnaire without assistance are being investigated (Bolling 1994). Finally, a study is under way to collect data from a larger, more diverse population to determine cutoff scores that will define clinically significant sexual dysfunction based on norms in a nonpatient population.

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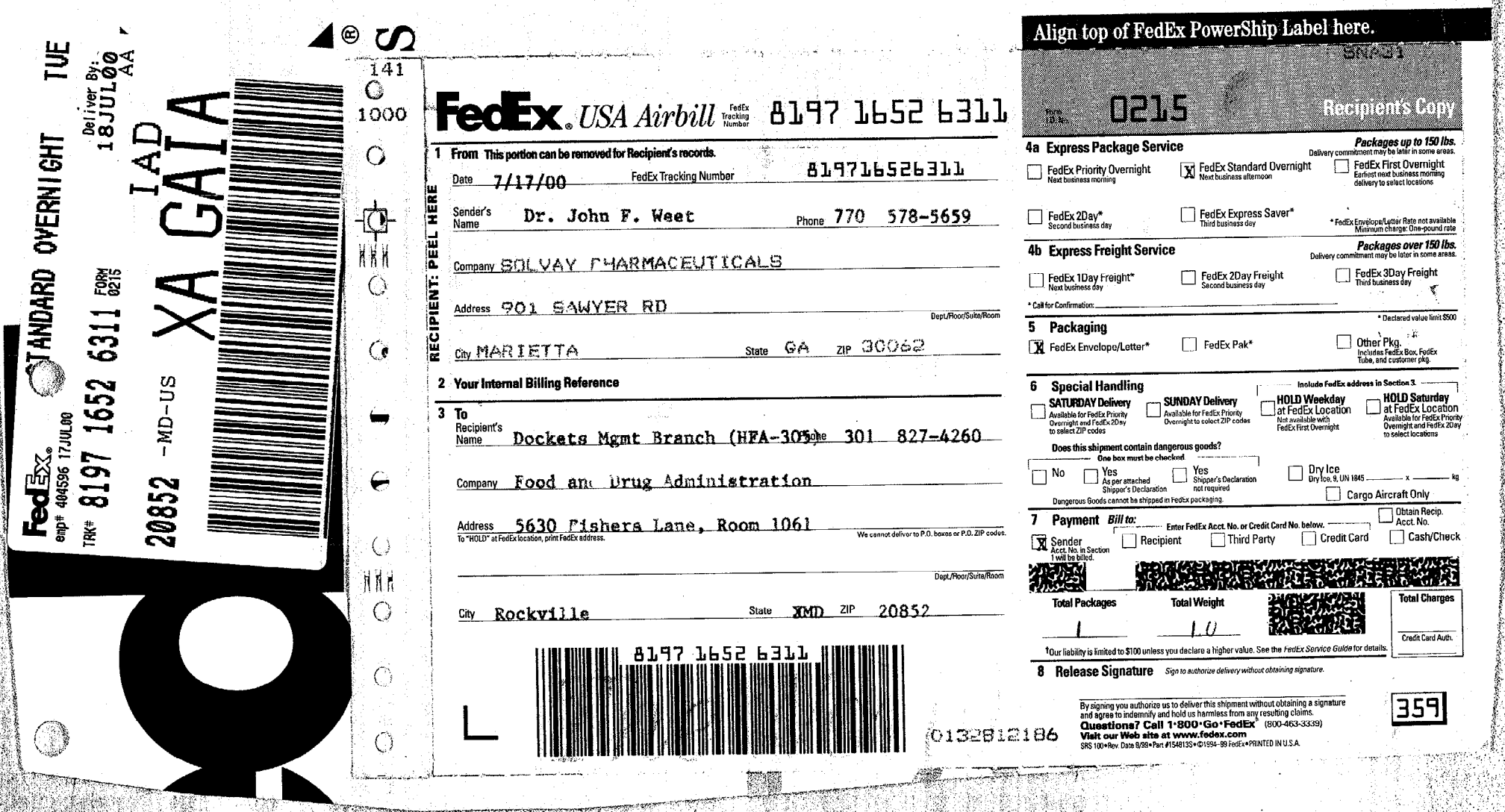

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Company SOLVAY PHARMACEUTICALS
Address 901 SAWYER RD Dept./Floor/Suite/Room
City MARIETTA State GA ZIP 30062

2 Your Internal Billing Reference

3 To
Recipient's Name Dockets Mgmt Branch (HFA-305) Phone 301 827-4260
Company Food and Drug Administration
Address 5630 Fishers Lane, Room 1061 Dept./Floor/Suite/Room
To "HOLD" at FedEx location, print FedEx address. We cannot deliver to P.O. boxes or P.O. ZIP codes.
City Rockville State MD ZIP 20852

8197 1652 6311
0132812186

Align top of FedEx PowerShip Label here.

SNP31
Form No. 0215 Recipient's Copy

4a Express Package Service — Packages up to 150 lbs. Delivery commitment may be later in some areas.
☐ FedEx Priority Overnight — Next business morning
☒ FedEx Standard Overnight — Next business afternoon
☐ FedEx First Overnight — Earliest next business morning delivery to select locations
☐ FedEx 2Day* — Second business day
☐ FedEx Express Saver* — Third business day
* FedEx Envelope/Letter Rate not available. Minimum charge: One-pound rate

4b Express Freight Service — Packages over 150 lbs. Delivery commitment may be later in some areas.
☐ FedEx 1Day Freight* — Next business day
☐ FedEx 2Day Freight — Second business day
☐ FedEx 3Day Freight — Third business day
* Call for Confirmation:

5 Packaging — * Declared value limit $500
☒ FedEx Envelope/Letter*
☐ FedEx Pak*
☐ Other Pkg. — Includes FedEx Box, FedEx Tube, and customer pkg.

6 Special Handling — Include FedEx address in Section 3.
☐ SATURDAY Delivery — Available for FedEx Priority Overnight and FedEx 2Day to select ZIP codes
☐ SUNDAY Delivery — Available for FedEx Priority Overnight to select ZIP codes
☐ HOLD Weekday at FedEx Location — Not available with FedEx First Overnight
☐ HOLD Saturday at FedEx Location — Available for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods? One box must be checked
☐ No
☐ Yes — As per attached Shipper's Declaration
☐ Yes — Shipper's Declaration not required
☐ Dry Ice — Dry Ice, 9, UN 1845 ____ x ____ kg
Dangerous Goods cannot be shipped in FedEx packaging.
☐ Cargo Aircraft Only

7 Payment Bill to: — Enter FedEx Acct. No. or Credit Card No. below.
☒ Sender — Acct. No. in Section 1 will be billed.
☐ Recipient
☐ Third Party
☐ Credit Card
☐ Cash/Check
☐ Obtain Recip. Acct. No.

Total Packages: 1
Total Weight: 1.0
Total Charges
Credit Card Auth.

†Our liability is limited to $100 unless you declare a higher value. See the *FedEx Service Guide* for details.

8 Release Signature — Sign to authorize delivery without obtaining signature.
By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.
Questions? Call 1·800·Go·FedEx® (800-463-3339)
Visit our Web site at www.fedex.com
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